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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/637,159	WEBER ET AL.	
	Examiner	Art Unit	
	IQBAL H. CHOWDHURY	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2008*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 24-34* is/are pending in the application.

4a) Of the above claim(s) *2-7,12-14 and 27-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 8-11, 18-19, 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 1-19 and 24-34 are currently pending.

In response to a previous Office action, a non-final action (mailed on 10/30/2007), Applicants filed a response and amendment received on May 29, 2008, amending claims 1 and 26, and canceling claims 20-23 is acknowledged. Claims 2-7, 12-14 and 27-34 remain withdrawn as directed to non-elected inventions.

Claims 1, 8-11, 18-19 and 24-26 are under consideration and are present for examination.

Applicants' arguments filed on May 29, 2008, have been fully considered but are not deemed persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim objection

Claim 18 is objected to as claim 18 depends on cancelled claim 17. Appropriate correction is required.

Claim 19 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 19 is not further

limiting of claim 18 because claim 18 is directed to a method of using a specific microorganism, whereas claim 19 is directed to a method of using a broader genus of microorganisms. As such, claim 19 broadens the scope of claim 18. Appropriate correction is required.

Claim 1 is objected to in the recitation "when compared to production ---- compound from the cell wherein", which should be "when compared to production ---- compound by the corresponding cell wherein". Appropriate correction is required.

New-Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 8-11 and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite in the recitation of "an activity of methylmalonyl-CoA mutase" polypeptide, as it is unclear what the scope of activities that is encompassed by this term. A polypeptide can have multiple activities such as enzymatic activity or binding activity to antibody of said polypeptide. The specification does not define the activity encompassed by this term. Therefore, the scope of the phrase "an activity" is vague and indefinite. Accordingly, claims 8-11 and 18-19 are rejected, as they are dependent on claim 1.

Claim 1, 8-11, 18-19 and 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention. Claim 1 is indefinite in the recitation of "animal feed promotant" as it is unclear what the meaning of the term promotant is. The specification does not define "promotant" in the context of animal feed. Therefore, the scope of the phrase "animal feed promotant" is vague and indefinite. Accordingly, claims 8-11, 18-19 and 24-26 are also rejected, as they depend on claim 1.

Withdrawn-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Previous rejection of Claims 1, 8-11, 18-19 and 24-26 under 35 U.S.C. 112, first paragraph on scope of enablement in view of applicants amendment of claim 1 by adding limitations of biological active compounds.

New-Claim Rejections - 35 USC § 112(1)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8-11, 18-19 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention.

These claims are directed to (1) a method of increasing the production of a biologically active compound in a Saccharopolyspora, Aeromicrobium or Streptomyces cell wherein the biologically active compound is derived from methylmalonyl-CoA, the method comprising the step of inhibiting by any means an activity of any methylmalonyl-CoA mutase (MCM) enzyme from any strain of Saccharopolyspora, Aeromicrobium or Streptomyces, or (2) a method of increasing the production of a biologically active compound in a Saccharopolyspora, Aeromicrobium or Streptomyces cell wherein the biologically active compound is derived from methylmalonyl-CoA, the method comprising the step of reducing by any means the transcription of a cob(I)alamin adenosyltransferase gene from any strain of Saccharopolyspora, Aeromicrobium or Streptomyces by any method.

The claims are drawn to a process of inhibiting a genus of MCM enzymes whose structures are not fully described in the specification. Similarly, the claims are drawn to a process of inhibiting the transcription of a genus of cob(I)alamin adenosyltransferase genes whose structures are not fully described in the specification. No information, beyond the characterization of a single MCM enzyme and cob(I)alamin adenosyltransferase, has been disclosed with regard to the structure of other MCM enzymes or cob(I)alamin adenosyltransferase genes from any strain of Saccharopolyspora, Aeromicrobium or Streptomyces, or additional methods to inhibit the enzymatic activity of said enzymes or the transcription of said cob(I)alamin adenosyltransferase genes. The claims as written encompass inhibition by any means

including mutating the gene encoding said MCM enzyme, which results in an inactive enzyme, reducing the promoter activity of the MCM gene by reducing transcription either by using a chemical inhibitor or expression of a protein which inhibits said MCM gene promoter activity, using antisense RNA or RNAi, reducing the cofactor coenzyme B12 by any means, reducing the transcription of a cobalamin adenosyltransferase (cob) gene by any means. The specification does not contain any disclosure of the structures of all the MCM enzymes or cob(I)alamin adenosyltransferase genes encompassed by the claims. The genus of polypeptides/genes recited is a large variable genus which can have wide variety structures. Therefore, many structurally unrelated enzymes/genes are encompassed within the scope of these claims. The specification discloses the structure of only a single representative species of the claimed genus, i.e. methylmalonyl-CoA mutase (MCM) protein encoded by SEQ ID NO 1 isolated from Aeromicrobium erythreum and a cobalamin adenosyltransferase protein encoded by SEQ ID NO: 3, wherein the inhibition was achieved by inhibiting the transcription by mutating said genes (such that the cofactor for MCM is reduced due to inhibiting transcription of SEQ ID NO: 3), which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the recited genus of enzymes/genes, methods to inactivate an enzyme and methods to inhibit transcription of a gene . Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Maintained-Claim Rejections - 35 USC § 112

Previous rejection of Claims 1, 8-11, 18-19, 24-26 under 35 U.S.C. 112, first paragraph, on scope of enablement rejection is maintained. This rejection has been discussed at length in the previous office action. The rejection is maintained for the following reasons.

The specification, while being enabling for a method of increasing the production of erythromycin in Aeromicrobium erythreum, wherein said erythromycin is derived from methylmalonyl-CoA and the method comprises inhibiting the activity of a methylmalonyl-CoA mutase (MCM) protein encoded by SEQ ID NO 1 from Aeromicrobium erythreum by either inactivating the MCM gene of SEQ ID NO: 1 or the cob gene of SEQ ID NO: 3 by transposon insertional mutation, does not reasonably provide enablement for a method of increasing the production of a biologically active compound in any Saccharopolyspora, Aeromicrobium or Streptomyces strains, wherein the biologically active compound is derived at least in part from methylmalonyl-CoA and the method comprises inhibiting the activity of the endogenous methylmalonyl-CoA mutase (MCM) enzyme in said strains by any means, reducing the levels of coenzyme B12 by any means, or inhibiting transcription of the cob(I)alamin adenosyltransferase gene in said strains by any means. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use** the invention commensurate in scope with these claims.

Applicants argue that the rejection has been obviated by cancelling claims 15-17 and 20-23, and by amending claim 1 to: (1) specify the cells; (2) clarify the biologically active compound, (3) clarify "increase," and (4) delete "in part" from modifying "methyl malonyl CoA."

Applicant's amendment to the claims and arguments have been fully considered but are not deemed persuasive to overcome the rejection on scope of enablement issues.

The claims still require a broad genus of MCM and cobA genes as well as a broad genus of methods for inhibiting the enzymatic activity of the MCM protein and a broad genus of methods for inhibiting transcription of the cobA gene. it is noted that even if the claims were to be limited to a method where the MCM enzymatic activity is eliminated by introducing an insertion in the coding region of the gene encoding the MCM protein, or by introducing an insertion in the coding region of the cobA gene in the strains recited, the claims would not be enabled in view of the fact that for homologous recombination to occur (needed for introducing an insertion), some knowledge of the structural features of the target MCM and cobA genes is required, No correlation between structure and function has been presented. In the instant case, there is no information as to the structural features required in any MCM or cob gene from any Saccharopolyspora or Aeromicrobium or Streptomyces strains, and neither the specification nor the art provide any information as to the degree of structural variability associated with these genes in the strains recited. As known in the art, the amino acid sequence of a protein determines its structural and functional properties. The art also

teaches how small variations in structure can result in major changes in function. Whisstock et al. (2003) teach that prediction of protein function from sequence and structure is a difficult problem because homologous proteins often have different functions (see abstract). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions. Similarly, at the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (1991 teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (1999) and Seffernick et al. (2001), where it is shown that even small amino acid changes result in enzymatic activity changes. Therefore, in view of the fact that a priori determination of function based solely on structural homology is highly unpredictable, one of skill in the art is left with the task of testing any number of proteins from these strains and determine which ones encode proteins having the desired function.

It should be noted that while the claims encompass a method where the production of a biologically active compound is increased in any Saccharopolyspora or

Aeromicrobium or Streptomyces strain by disrupting the MCM gene, the art, as evidenced by Vrijbloed et al. (1999, see PTO-892) teaches that simply disrupting this gene may not be sufficient to observe an increase in the production of a biologically active compound as recited by the claims. As taught by Vrijbloed et al., a S. cinnamonensis mutB mutant (mutant comprising a disruption in the MCM gene) produced similar levels of a biologically active compound (monensin A) compared to the wild type strain lacking the disruption (page 5602, left column, first 4 lines). Thus, it appears that it may be unpredictable as to whether simply disrupting the MCM gene in the recited microorganisms would result in increased production of a desired biologically active compound as claimed.

The claims are also still broad with regard to the methods of inhibition of the MCM enzyme or methods of inhibition of transcription of a cob(I)alamin adenosyltransferase gene. While such inhibition encompasses, for example, mutations in the MCM gene which result in an inactive enzyme, reduction in the promoter activity of the MCM gene by reducing transcription, using, for example, antisense RNA or RNAi of MCM mRNA, reduction in the production of the cofactor coenzyme B12 by any means, and reduction in transcription of the cob(I)alamin adenosyltransferase gene by any means, the specification merely provides a single method to inactivate activity and inhibit transcription of a gene, i.e., introduction of an insertion in the gene of interest.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and means of inhibition of said MCM

enzyme and inhibition of transcription of the cob gene, and the high degree of unpredictability of the prior art in regard to determining a priori the function of a protein based solely on structural homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Therefore, the rejection is maintained.

Withdrawn-Claim Rejections - 35 USC § 102

Previous rejection of Claims 1, 8-11 and 24-26 under 35 U.S.C. 102(b) as being anticipated by Vrijbloed et al. (J Bacteriol. 1999 Sep; 181(18): 5600-5) is withdrawn in view of applicants amendment of claims and persuasive arguments.

Withdrawn-Claim Rejections - 35 USC § 103

Previous rejection of Claim 18 under 35 U.S.C. 103(a) as being unpatentable over Vrijbloed et al. (J Bacteriol. 1999 Sep; 181(18): 5600-5) as applied to claims 1-17, 19, 27-31 above, and further in view of Katz et al. (Novel macrolides through genetic engineering, Med Res Rev. 1999 Nov; 19(6): 543-58. Review) is withdrawn in view of applicant's amendment of claims and persuasive arguments.

Conclusion

Status of the claims:

Claims 1-19 and 24-34 are currently pending. .

Claims 2-7, 12-14 and 27-34 are withdrawn.

Claims 1, 8-11, 18-19 and 24-26 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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